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MOLECULAR-SIZED CHANNELS AND FLOWS
AGAINST THE GRADIENT

by

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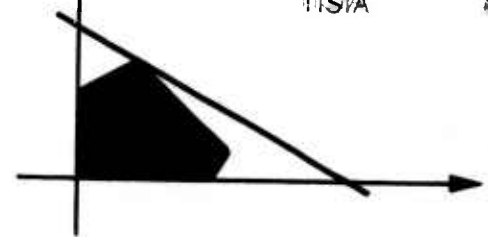
MOLECULAR-SIZED CHANNELS AND FLOWS AGAINST THE GRADIENT

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MOLECULAR-SIZED CHANNELS AND FLOWS AGAINST THE GRADIENT *

SUMMARY:

If a passage is so narrow that species must line up in it in single file, then a Markov-type process can take place in which several species considered together would have an average flow from their high to low total concentration, but some subset of the species could have an average flow against their individual gradients. Hodgkin and Keynes (J.Physiol., Vol.128, 1955) proposed this type of model to explain observed exchange rates of potassium and its labelled isotope across the membrane of a living cell. We extend this approach by assuming that there are particles of different types (e.g., Na^+, K^+, H_2O) which compete for entry into a passage.

Consider a passage interconnecting two compartments A and B that is so narrow that n objects must line up in single file in the passage. The objects originating in A will be denoted by a , those in B by b . In the figure, n = 7 and there are three objects from A and four from B .
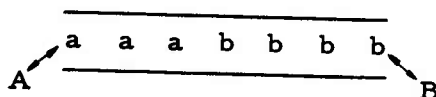
We will call the number of a objects in the passage the state. In the above case, the state is 3 . The state of the passage can be changed however by the impact of an a object from A or by the impact of a b object from B . If impacts occur simultaneously at both ends, no change takes place. If not, we refer to the impact as an a impact-event if it is caused by an a object, and as a b impact-event in the other case. Only if the state is 0 can a b impact-event cause an object b to be driven out of the passage and

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become an object of A , or, if the state is n , can an <u>a</u> impact-event cause an object <u>a</u> to become an object of B . We are interested in the relative frequency of the events "an <u>a</u> object moves into the B compartment" and "a <u>b</u> object moves into the A compartment."

THEOREM: If the relative frequency of <u>a</u> impact-events to <u>b</u> impact-events is λ , then the ratio of the probabilities of the events "an <u>a</u> object moves into B" and "a <u>b</u> object moves into A" is $r = \lambda^{n+1}$, and the difference of their probabilities is $(1 - \lambda)/(1 + \lambda)$.

COROLLARY: The probability of a flow from B to A after an impact-event is $\frac{1 - \lambda}{1 + \lambda} \cdot \frac{1}{1 - \lambda^{n+1}}$; the probability of the reverse flow is $\frac{1 - \lambda}{1 + \lambda} \cdot \frac{\lambda^{n+1}}{1 - \lambda^{n+1}}$; for $n \to \infty$ and $\lambda < 1$, the former tends to $(1 - \lambda)/(1 + \lambda)$ and the latter to 0 . (If λ is close to unity, $(1 - \lambda)/(1 + \lambda)$ may be replaced by $\frac{1}{2}(1 - \lambda)$ in an approximation.)

PROOF: Let $n = 3$ (to simplify discussion) and let p be the probability of an <u>a</u> impact-event and $q = 1 - p$ be the probability of a <u>b</u> impact event. Then

$$\lambda = \frac{p}{q} \quad , \quad p = \frac{\lambda}{1 + \lambda} \quad , \quad \text{and} \quad q = \frac{1}{1 + \lambda} \quad .$$

Let x_i be the probability that, after a long sequence of events, the passage is in state i , where $i = 0, 1, 2, \ldots, n$. Then

(1) $$x_0 + x_1 + x_2 + x_3 = 1 \quad , \qquad x_i \geq 0 \quad .$$

The matrix below gives the transition probabilities of going from state i to j after an event.

State before an event	State after an event			
	0	1	2	3
0	q	p		
1	q	0	p	
2		q	0	p
3			q	p

The probabilities of being in various states satisfy

$$qx_0 + qx_1 = x_0$$
$$px_0 + qx_2 = x_1$$
$$px_1 + qx_3 = x_2$$
$$px_2 + px_3 = x_3 \quad .$$

By combining terms, we obtain

$$-px_0 + qx_1 = 0$$
$$px_0 - x_1 + qx_2 = 0$$
$$px_1 - x_2 + qx_3 = 0$$
$$px_2 - qx_3 = 0 \quad .$$

If now we add the first equation to the second, the modified second to the third, and drop the last equation as redundant (it is the same as the modified third), we obtain

$$-px_0 + qx_1 = 0$$
$$- px_1 + qx_2 = 0$$
$$- px_2 + qx_3 = 0 \quad .$$

It follows that

$$x_1 = \lambda x_0 \quad , \quad x_2 = \lambda^2 x_0 \quad , \quad x_3 = \lambda^3 x_0 \quad ,$$

where $\lambda = p/q$. Substituting in (1), x_0 is given by

$$x_0(1 + \lambda + \lambda^2 + \lambda^3) = 1 \quad \text{or} \quad x_0 = \frac{1 - \lambda}{1 - \lambda^4} \quad .$$

The probabilities that an $\underline{a}$ object moves into B and that a $\underline{b}$ object moves into A are respectively

$$px_3 = \frac{1 - \lambda}{1 - \lambda^4} \cdot \lambda^3 \cdot \frac{\lambda}{1 + \lambda}$$

and

$$qx_0 = \frac{1 - \lambda}{1 - \lambda^4} \cdot \frac{1}{1 + \lambda} \quad ;$$

hence their ratio r is

$$r = \frac{px_3}{qx_0} = \frac{p\lambda^3 x_0}{qx_0} = \lambda^4 \quad ;$$

and, in general

$$px_n = \frac{1 - \lambda}{1 - \lambda^{n+1}} \cdot \lambda^{n+1} \cdot \frac{1}{1 + \lambda} \quad ; \quad qx_0 = \frac{1 - \lambda}{1 - \lambda^{n+1}} \cdot \frac{1}{1 + \lambda} \quad ,$$

$$r = \frac{px_n}{qx_0} = \lambda^{n+1} \quad , \quad px_n - qx_0 = \frac{1 - \lambda}{1 + \lambda}$$

establishing the theorem and its corollary.[*]

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[*] R. Oliver has provided the author with an alternative proof based on a continuous Markov process.

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Let C_a be the concentration of <u>a</u> objects in A and C_b the concentration of <u>b</u> objects in B . Assuming that the number of impact-events per unit time is proportional to the concentration, with the <u>same</u> proportionality factor μ for each type of object, then

$$\lambda = p/q = C_a/C_b$$

and the flow F_a from A to B and the flow F_b from B to A are given by

$$F_a = \mu C_a x_n = \mu C_a \frac{\lambda^n(1 - \lambda)}{1 - \lambda^{n+1}} = \mu \frac{\lambda^{-1} - 1}{\lambda^{-(n+1)} - 1} C_a$$

$$F_b = \mu C_b x_0 = \mu C_b \frac{(1 - \lambda)}{1 - \lambda^{n+1}} = \mu \frac{1 - \lambda}{1 - \lambda^{n+1}} C_b \quad .$$

Subtracting the quantity of flow in one direction from the other and setting $C_a = \lambda C_b$, we obtain

$$F_b - F_a = \mu C_b x_0 - \mu C_a x_n = \mu C_b(1 - \lambda) = \mu(C_b - C_a) \quad ,$$

whereas the ratio of flow rates r is given by

$$r = F_a/F_b = (C_a/C_b)^{n+1} \quad .$$

THEOREM: If the number of impact-events of objects <u>a</u> in A or <u>b</u> in B is proportional to their concentrations C_a in A or C_b in B with the <u>same</u> proportionality factor μ , then the difference of their flow rates is $\mu(C_b - C_a)$ which is independent of the "length" n of the passage, while the ratio of their flow rates r is given by $(C_a/C_b)^{n+1}$, the $n+1^{st}$ power of the ratio of their concentrations.

If there is a charge potential between the two sides with voltages E_A in A and E_B in B , we would expect, in the case of positively charged $\underline{a}$, $\underline{b}$ objects, that the number of impact-events will be proportionally higher per unit of concentration on side A if $(E_B - E_A) < 0$. We shall assume in this case that

$$\lambda^* = C_a^* / C_b^*$$

where C_a^* and C_b^* are the values of C_a and C_b adjusted for charge effects; for example we might set

$$C_a^* \doteq C_a e^{-\pi/2}$$

$$C_b^* \doteq C_b e^{+\pi/2} \quad ,$$

where $\pi = (RT/F)(E_B - E_A)$ and (RT/F) is a physical constant. In this case, the formulæ for flow become

$$F_a = \mu \frac{(\lambda^*)^{-1} - 1}{(\lambda^*)^{-(n+1)} - 1} C_a^*$$

$$F_b = \mu \frac{1 - (\lambda^*)}{1 - (\lambda^*)^{n+1}} C_b^* \quad .$$

The sign of π above is reversed in case of negatively charged $\underline{a}$, $\underline{b}$ objects.

Reverse Gradient Flows

Let us now suppose that the A compartment really contains two kinds of $\underline{a}$ objects, K^+ and Na^+ , with concentrations C_K' and C_{Na}' . Similarly suppose that there are two kinds of $\underline{b}$ objects, also K^+ and Na^+ , but with concentrations C_K'' and C_{Na}'' in B . If we assume that numbers of impact-

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events on each side are proportional to these concentrations (see Comment 2), then

$$\lambda = \frac{p}{q} = \frac{C_K' + C_{Na}'}{C_K'' + C_{Na}''} \quad .$$

More generally, if Na^+ has relatively fewer impacts per unit of concentration than K^+, say with a reduction factor w, then

$$\lambda = \frac{p}{q} = \frac{C_K' + wC_{Na}'}{C_K'' + wC_{Na}''} \quad .$$

The table below gives the resulting probabilities for the four possible kinds of events, calculated by noting that the ratio of K^+ to Na^+ in the passage for $\underline{a}$ objects is C_K'/wC_{Na}' and that the ratio for $\underline{b}$ objects is C_K''/wC_{Na}''

	Flow from A to B	Flow from B to A
K^+	$x_n p \dfrac{C_K'}{C_K' + wC_{Na}'}$	$x_0 q \dfrac{C_K''}{C_K'' + wC_{Na}''}$
Na^+	$x_n p \dfrac{wC_{Na}'}{C_K' + wC_{Na}'}$	$x_0 q \dfrac{wC_{Na}''}{C_K'' + wC_{Na}''}$

Comparing the ratio of Na^+ flows in the direction A to B versus B to A, we have by the previous relation for λ,

$$r_{Na} = \frac{C_{Na}'}{C_{Na}''} \cdot \frac{x_n}{x_0} = \frac{C_{Na}'}{C_{Na}''} \cdot \lambda^n \quad .$$

It is now clear that, even if the concentration of Na^+ in A is less than in B (i.e., $C'_{Na} < C''_{Na}$), it is possible that the net flow of Na^+ will nevertheless be in the direction of A to B. Indeed, let $C'_K + wC'_{Na} > C''_K + wC''_{Na}$ so that their ratio, λ, is greater than 1; then, for a sufficiently long passage n, $\lambda^n > C''_{Na}/C'_{Na}$, resulting in $r_{Na} > 1$, i.e., a flow of Na^+ against the gradient.

Example 1: Let $w = 1$, $n = 4$ and let the relative concentrations be as indicated:

	Relative Concentrations in A	Relative Concentrations in B
K^+	19	1
Na^+	1	9
Total	20	10

$$\lambda = 20/10 = 2$$

$$r_{Na} = 1/9 \cdot 2^n = 1/9 \cdot 2^4 = 16/9 > 1$$

Thus Na^+ flows in the direction of greater concentration even though the concentration in B is nine times greater than in A. The passage holds only $n = 4$ objects.

Example 2: Let $w = 1$. Find n so that K^+ will back flow from B to A against a 19 to 1 gradient in a second passage admitting only H_2O and K^+.

	Relative Concentrations in A	Relative Concentrations in B
H_2O	.9950	.9900
K^+	.0001	.0019
Total	.9951	.9919

Thus

$$\lambda = \frac{9951}{9919} \quad .$$

We want $r_K = (1/19)\lambda^n > 1$, or

$$n \log \lambda > \log 19$$

$$n > \frac{\log 19}{\log 9951 - \log 9919}$$

$$> \frac{1.27875}{.99787 - .99647}$$

$$> \frac{1.27875}{.00140} = 913 \quad .$$

Example 3: Suppose Na^+ is allowed also to back flow, if possible, in the passage of Example 2, but its $w = w_{Na}$ weight is so small that it restricts the net flow of Na^+ from B to A to be very small relatively to the corresponding flow of K^+, in spite of a relative concentration in B to A of 9 to 1, as in Example 1. Since the relative net flow of K^+ to Na^+ in Example 1 is $(19 \times 2^4 - 1)/(1 \times 2^4 - 9) = 63$, the value of w_{Na} will have to be selected in a steady state situation so that the relative net back flow of K^+ to Na^+ in the second passage is also $63/1$. For some fixed value of $\lambda^n > 19$ (so that K^+ will back flow), say $\lambda^n = 20$, this can be easily done.

In order to make the back flow of K^+ 63 times greater than the flow of Na^+, we must also have

$$(\lambda^n - 19) = 63(9\lambda^n - 1)w_{Na} \quad ,$$

where the relative concentrations of Na^+ to K^+ in A and B are shown in Example 1.

Fixing $\lambda^n = 20$, say we have $w_{Na} = 1/(63 \times 179) = 8.86 \times 10^{-5} \doteq 9 \times 10^{-5}$

	Relative Concentrations in B	in A
H_2O	.995000	.990000
K^+	.000100	.001900
$(Na^+)w_{Na}$	.000000*	.000000*
Total	.995100	.991900

*$(9 \times 10^{-4}) \times (9 \times 10^{-5}) = 81 \times 10^{-9}$; $(10^{-4}) \times (9 \times 10^{-5}) = 9 \times 10^{-9}$

This yields

$$\lambda = \frac{.9951}{.9919}$$

$$n = \frac{\log 20}{\log .9951 - \log .9919}$$

$$= 929 \quad .$$

Comment 1: By assuming fluxing water in a narrow passage where only H_2O, K^+ and a small amount of Na^+ (relative to K^+) can enter, and by allowing K^+ and Na^+ to return through another passage where only these charged ions can enter, we have shown that it is possible to maintain the ratios of Na^+ and K^+ similar to those found typically in certain cells and plasma of living things.

Comment 2: The number of impact-events is assumed to be proportional to the relative concentrations in A to those in B. If these concentrations are high, such as that of H_2O in Example 2, then λ will turn out to be close to unity, and this will require n to be large, for flows against the gradient of Na^+ or K^+. Note, however, that even if $n \to \infty$, the probability of flow per impact-event from the higher total concentration compartment to the lower is always greater than 1/2 the difference in their total concentrations (measured

in mole fractions). In this case the probability is greater than $1/2$ (.9951 - .9919) = .0016 . Moreover, if high concentrations can be assumed to result in many impacts on both sides that are simultaneous, it may turn out safe to assume that λ is, in fact, significantly different from unity and that a "continuous" flow will result favoring that side with the higher total concentration, and thus permit any species which make up the total concentration to flow against its individual gradient.

Comment 3: If λ is unity, a long passage could act as an effective plug for holding apart the differential concentrations on either side. But small shifts of λ could easily be visualized as freeing the plug after some delay and setting up a flow favoring the side with higher total concentration.

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